

# EHCSS – E4

## Bibliography- Clinical Studies

PM3001372566

## ABSTRACT

### INVESTIGATION OF BIOMARKER OF EXPOSURE OF ADULT SMOKERS SMOKING ELECTRICALLY HEATED AND CONVENTIONAL CIGARETTES.

Hans J. Roethig, Robin Kinser, Bettie L. Nelson, Raymond W. Lau; Philip Morris, USA, Richmond, VA  
The electrically heated cigarette (EHC) is made of conventional tobacco filler rolled in a tobacco mat and smoked in a battery operated lighter, which heats the tobacco during puffing. When smoked in a smoking machine according to the FTC method the electrically heated cigarette (3mg tar, 0.2mg nicotine) showed marked reduction of CO in mainstream smoke as compared to a Kentucky standard reference cigarette, 1R4F. EHC-1 and EHC-2 have different filters. The purpose of the study was to determine whether CO in exhalate, CO-hemoglobin and nicotine and 5 major nicotine metabolites in 24 hour urine differ among smokers of EHC-1, EHC-2, CC (conventional cigarettes) and no-smoking. Study population: 110 healthy, adult male and female subjects smoking 5 - 25 CC (11mg tar, FTC) per day.

Study design: Controlled, randomized, stratified for gender and number of cigarettes smoked per day. After consenting, subjects were screened to meet inclusion and exclusion criteria. Eligible subjects were confined for 10 days to control for smoking (number of cigarettes per day and smoking times). Baseline investigations were on day -1, thereafter subjects were randomized to one of 5 groups: CC 11 mg tar; CC 3 mg tar; EHC-1; EHC-2; no-smoking.

Investigations: CO in exhalate was measured using a Micro Medical CO Meter, CO-hemoglobin was measured by spectrophotometry using a CO-Oximeter on day -1 (baseline), 3 and 8. Nicotine and metabolites in urine were determined by LC-MS/MS.

Data analysis: Data were calculated as change from baseline and compared between the groups.

CO and CO-hemoglobin were decreased by about 25 % when smokers were switched from CC 11 mg tar to CC 3 mg tar . CO and CO-hemoglobin showed levels comparable to no smoking after switching to EHC-1 and EHC-2. Nicotine and metabolite excretion in urine decreased in the CC 3 mg tar group, the EHC-1 and EHC-2 groups.

Poster at SRNT 2002

# Introduction

This study was performed to evaluate the exposure of adult smokers to nicotine and carbon monoxide from 4 different cigarettes, 2 conventional cigarettes of different tar categories and 2 electrically heated smoking systems (EHCSS) with different filters.

# Study Subjects

- Inclusion criteria:
  - Adult male and female *healthy* smokers
  - Smoking 5 - 25 conventional cigarettes (11 mg tar, 0.8 mg nicotine, FTC) per day
  - 21 - 65 years
- Exclusion criteria:
  - Pregnant or nursing women
  - Use of other nicotine products
  - $FEV_1 < 75 \%$

# Demographics

Trait				
<b>Gender</b>		<b>Female</b>	<b>Male</b>	<b>Overall</b>
		55	55	110
<b>Race</b>	American Indian	2	1	3
	Asian		3	3
	Black	2	1	3
	Caucasian	50	49	99
	Hispanic	1	1	2
<b>Frame Size</b>	Small	12	5	17
	Medium	35	36	71
	Large	8	14	22
<b>Age</b>	Mean	33	30	31
	Minimum	21	21	21
	Maximum	58	58	58
<b>Weight (lb)</b>	Mean	149.2	176.7	163.0
	Minimum	104.0	125.0	104.0
	Maximum	227.0	245.0	245.0
<b>Height (in)</b>	Mean	65.9	70.7	68.3
	Minimum	59.0	66.0	59.0
	Maximum	71.0	76.0	76.0

# Study Design

- Open, Randomized Controlled Trial
  - Stratified for gender and number of cigarettes per day (5-10, 11-20, 21-25)
- 5 Parallel groups
  - 20 subjects per group
  - 10 days confinement

# Study Schedule

- Days -30 to -3: Screening
- Day -3: Confinement in the evening
- Day -2: Acclimation
  - Smoking **conventional cigarette 1** (11 mg tar, 0.8 mg nicotine, FTC)
  - Subjects were allowed to smoke as many cigarettes as reported in their smoking history plus 20 %.
  - Subjects were monitored for actual cigarette consumption to determine their daily allotment for the remainder of the study (days 1 - 8). This determined the *maximum daily allowance* (6 - 30 cigarettes per day).

# Study Schedule

- Day -2: Acclimation
  - Smoking was only allowed at *predetermined smoking times* from 7 AM to 11 PM. (every 32 minutes, maximally 30 smoking times).
  - Cigarettes were smoked evenly over the day.
- Day -1: Baseline investigations
  - *Controlled* smoking of **conventional cigarette 1**
- Day -1: Randomization
  - Subjects were randomized into one of 5 groups and moved to 5 separate study rooms according to their group allocation:
    - A. continue smoking of **conventional cigarette 1** (11 mg tar)
    - B. switch to **conventional cigarette 2** (3 mg tar)
    - C. switch to **EHCSS 1** (3 mg tar)
    - D. switch to **EHCSS 2** (2 mg tar)
    - E. switch to **no-smoking**



# Study Schedule

- Days 1 - 8:
  - Controlled Smoking (groups A-D) for 8 days
  - Cigarettes were smoked evenly over the day.
- Day 8: Final Investigations

# Investigational Products

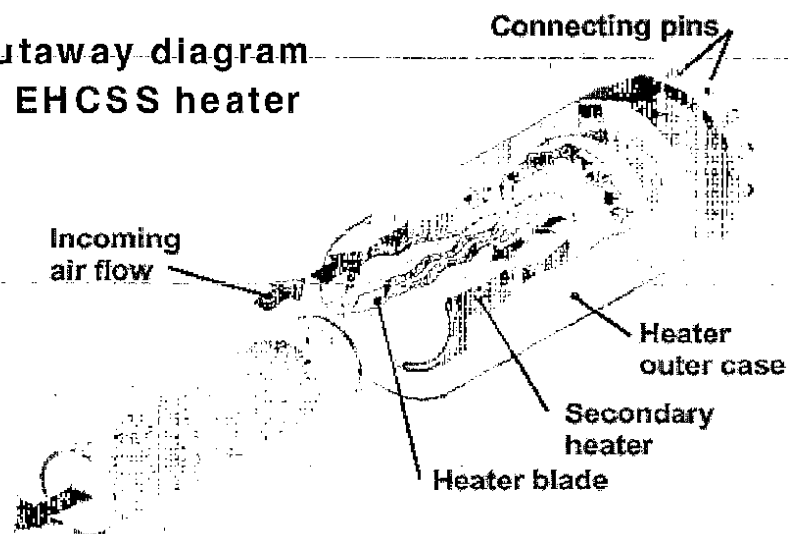
## Mainstream Smoke

(Data from smoking machines, FTC)

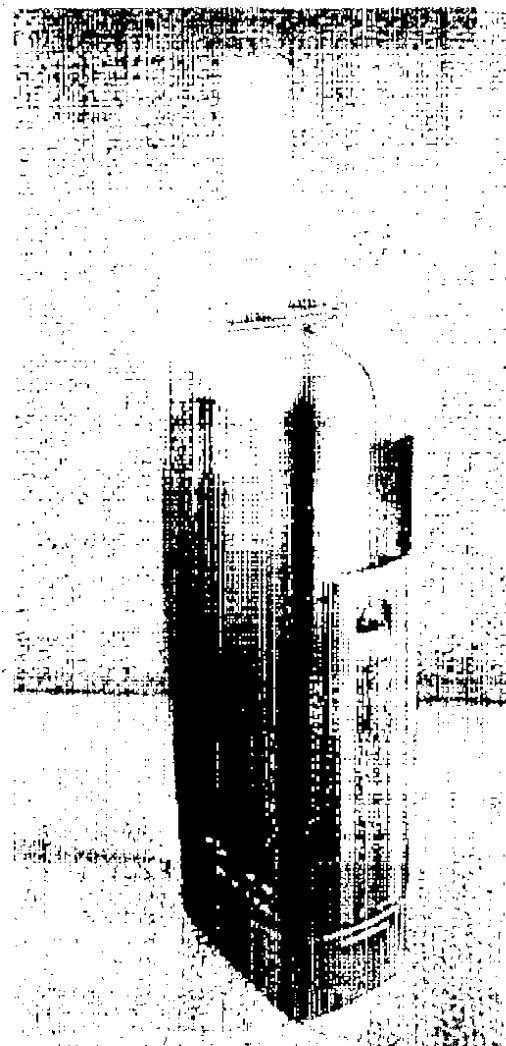
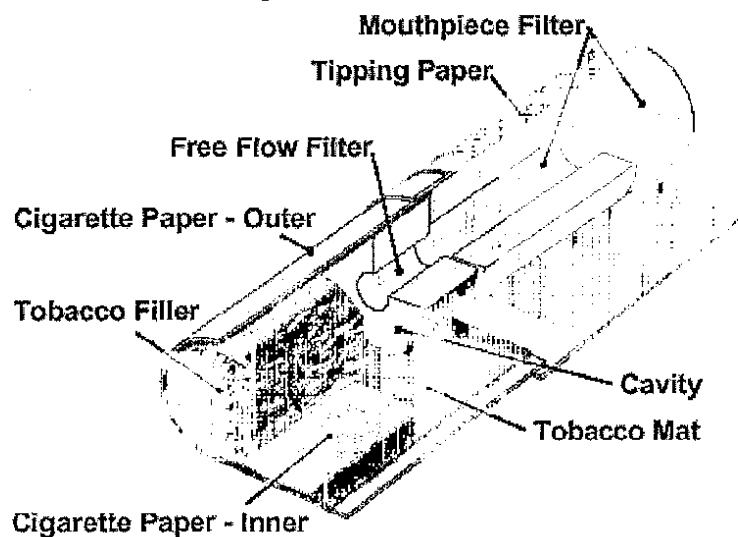
(mg per cigarette)	Tar	Nicotine	CO
A. Conventional Cigarette 1	11	0.8	12
B. Conventional Cigarette 2	3	0.3	4
C. EHCSS 1	3	0.2	0.7
D. EHCSS 2	2	0.2	0.7

# Electrically Heated Cigarette Smoking System

Cutaway diagram  
of EHCSS heater



EHCSS Cigarette Construction



# Investigations

- Screening
  - Medical and smoking history, questionnaire, physical, routine labs, pregnancy test, EKG, FEV<sub>1</sub>, drugs of abuse, HIV, Hepatitis B and C
- Days -1, 3 and 8
  - Biomarkers of exposure
    - Nicotine and 5 metabolites (nicotine-N-glucuronide, cotinine, cotinine-N-glucuronide, *trans*-3'-hydroxycotinine, *trans*-3'-hydroxycotinine-O-glucuronide) in 24-hour-urine, the sum, on a molar basis, presented as nicotine-equivalents, measured by LC/MS/MS
    - Biomarkers estimating biological effective dose
    - CO-hemoglobin in blood measured by spectrophotometry

# Data Evaluation

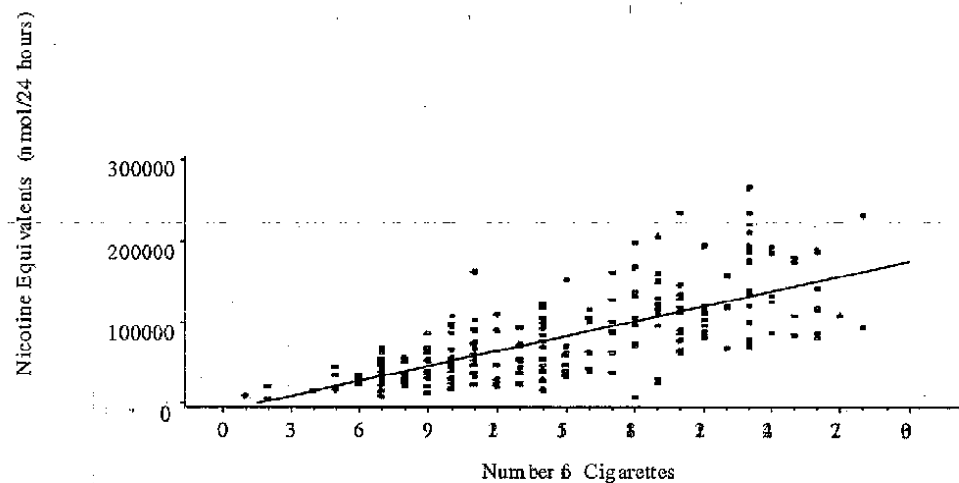
- Response variables:
  - Change from baseline (day - 1) on day 3 and 8
- Descriptive statistics per group
- Comparisons between the 5 groups

# Nicotine Equivalents in Urine ( $\mu$ moles/24hrs)

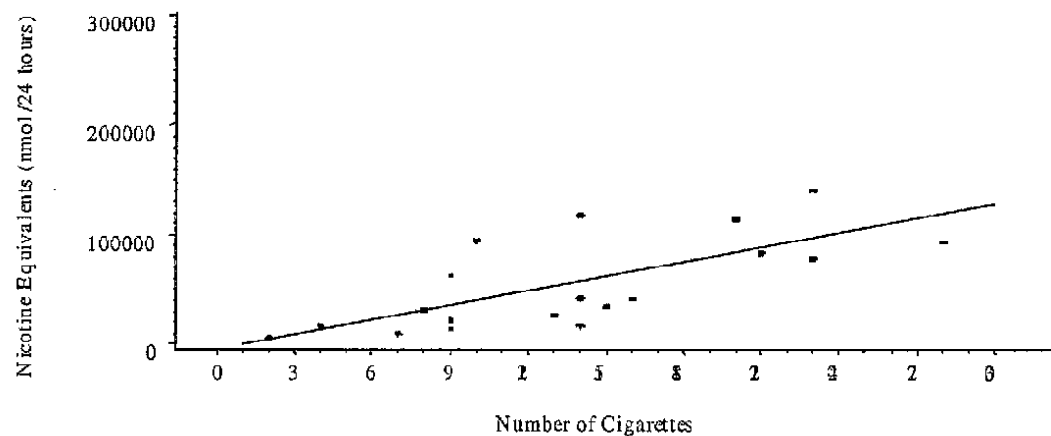
Study Group	Day -1	Day 3	Day 8
Conventional Cigarette 1	89.5	84.8	66.8
Conventional Cigarette 2	99.5	77.1	58.0
EHCSS 1	79.4	39.5	22.9
EHCSS 2	102.9	37.6	36.1
No-Smoking	96.5	8.2	0.3

# Daily Nicotine Equivalent Excretion

## Conventional Cigarette 1, Baseline (Day -1)



## Conventional Cigarette 2, Day 8

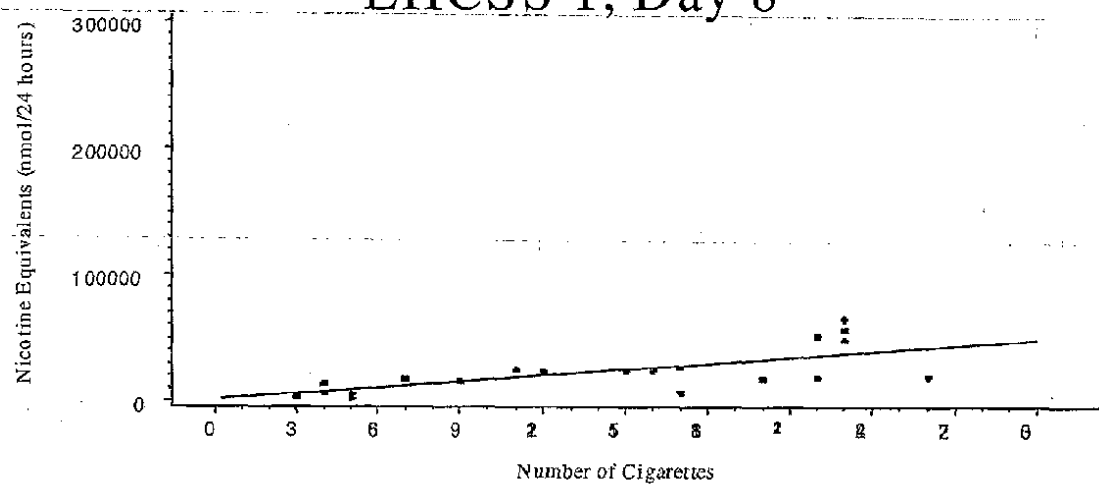


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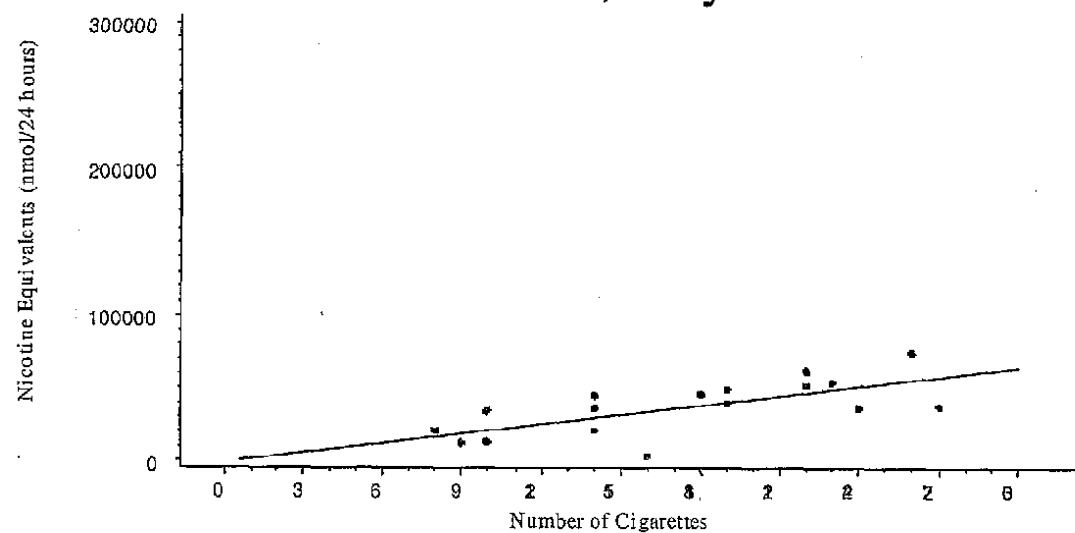
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# Daily Nicotine Equivalent Excretion

## EHCSS 1, Day 8



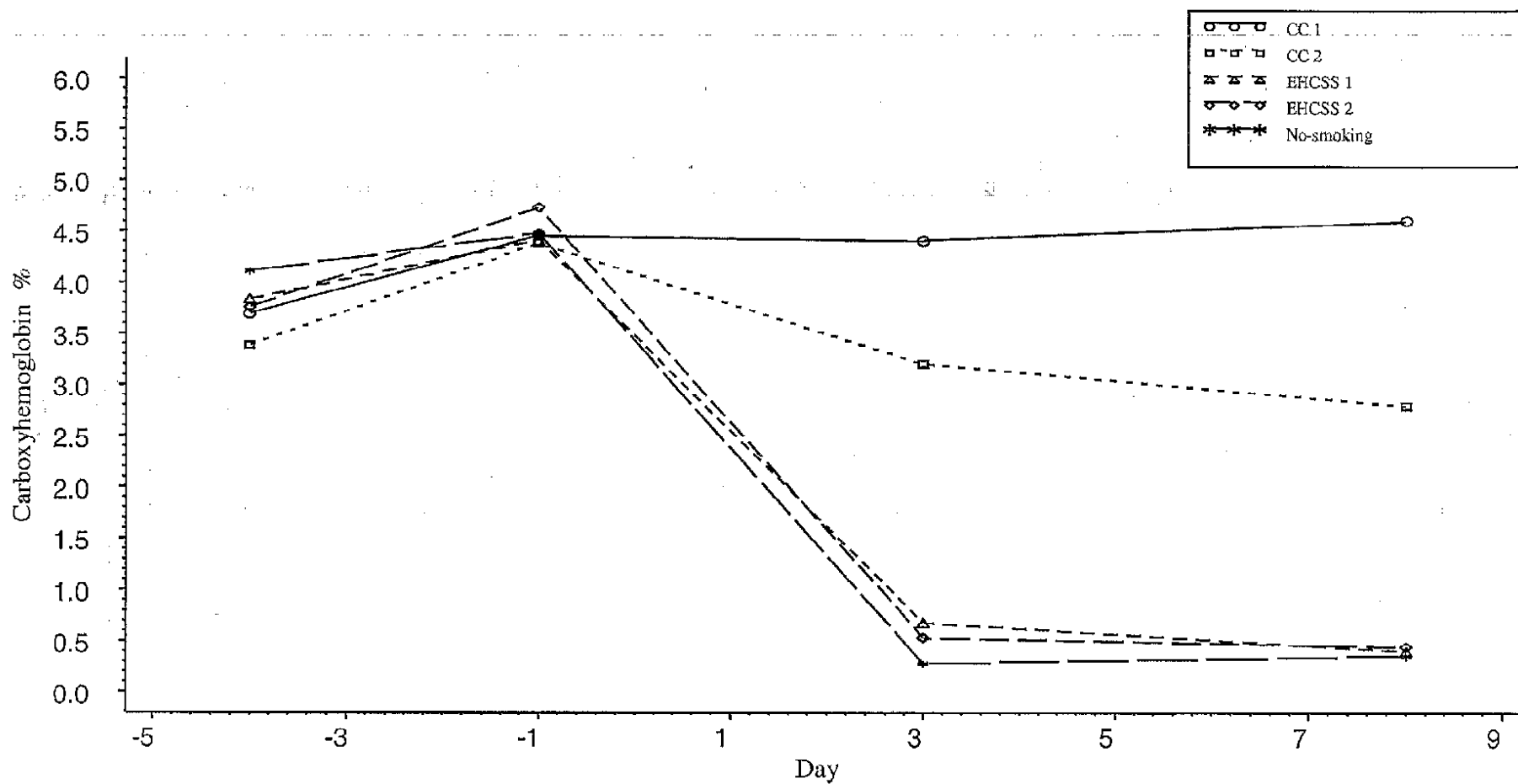
## EHCSS 2, Day 8



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# Mean Carboxyhemoglobin

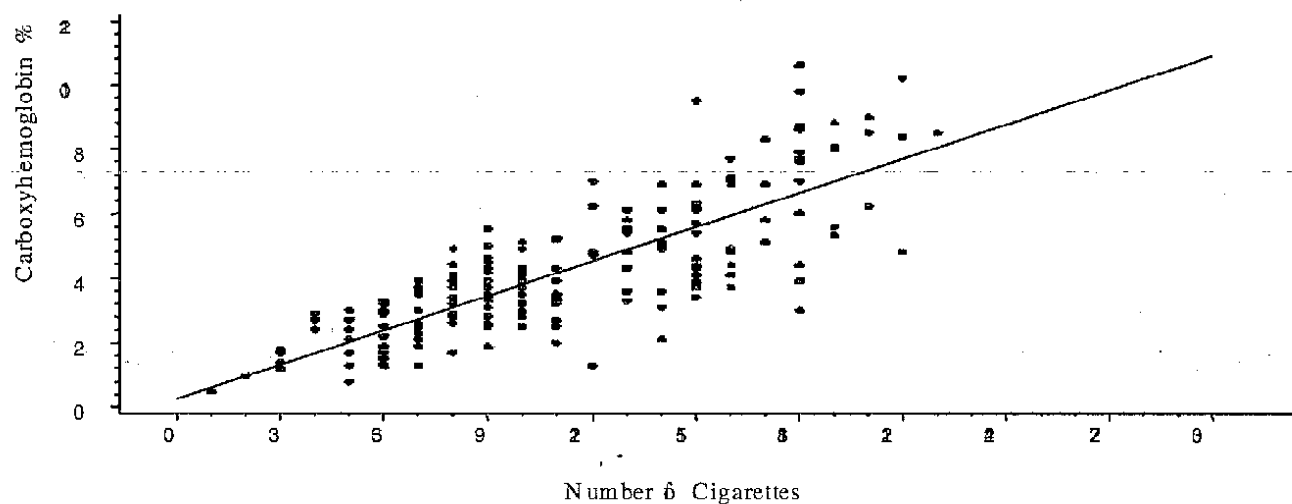


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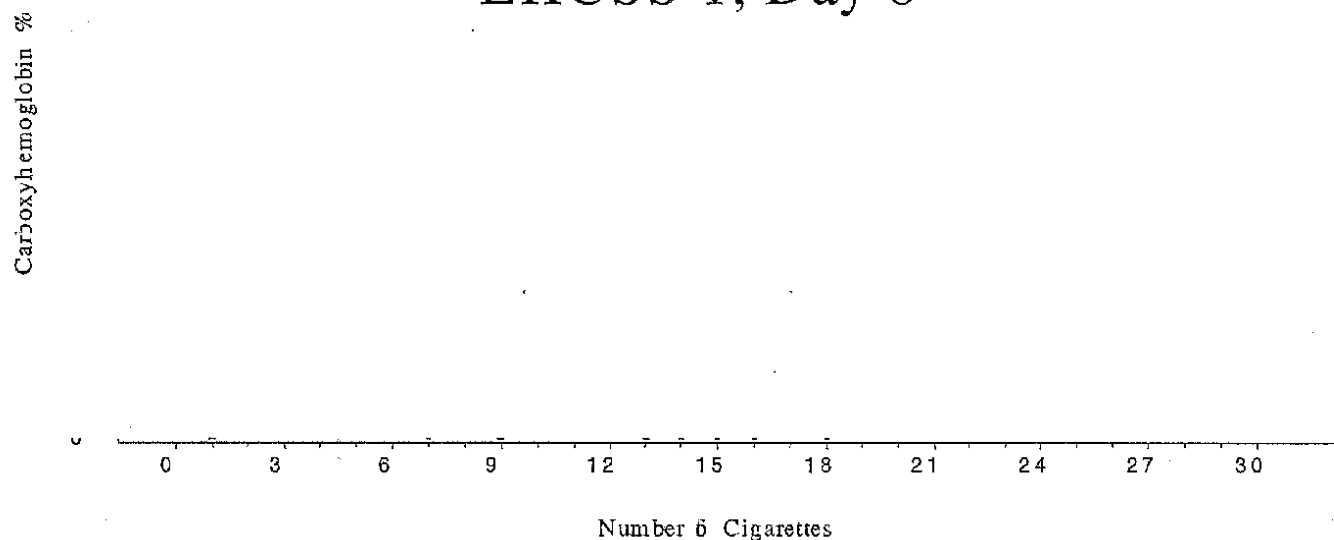
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# Carboxyhemoglobin

## Conventional Cigarette 1, Baseline (Day -1)



EHCSS 1, Day 8



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## Carboxyhemoglobin and Nicotine Equivalent Excretion, Change from Baseline (% Change)

<b>Study Group</b>	<b>Day 3 COHb</b>	<b>Day 3 NicEquiv</b>	<b>Day 8 COHb</b>	<b>Day 8 NicEquiv</b>
Conventional Cigarette 1	-0.1 (-1.3)	-9.8 (-6.3)	+0.3 (+6.3)	-22.5 (-25)
Conventional Cigarette 2	-1.2 (-27.3)	-22.4 (-23)	-1.6 (-37.4)	-41.5 (-42)
EHCSS 1	-3.7 (-84.1)	-39.9 (-50)	-4.1 (-94)	-56.5 (-71)
EHCSS 2	-4.3 (-92)	-65 (-64)	-4.5 (-96)	-66.8 (-65)
No-Smoking	-4.2 (-93)	-88.4 (-92)	-4.3 (-96)	-96.2 (-99.7)

## Conclusions

After 8 days of smoking an electrically heated cigarette, carboxyhemoglobin levels in adult smoking subjects were in the same range as those from subjects not smoking for 8 days.